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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	Kevin P. Baker	P2548P1C8	2448

7590 03/24/2003

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

13

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BAKER ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 22-34 are pending in the instant application. Claims 1-21 have been canceled and claims 22-34 have been added as requested by Applicant in Paper Number 4, filed August 30, 2001.

Specification

2.1 The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. See page 25, line 10, page 27, line 31 and page 94, line 32. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

2.2 The disclosure is also objected to because the tables are not labeled consecutively. The first table is Table 6 on page, 61, then tables 7-10 on pages 85, 96, 122 and 137, and then the last two tables are Tables 23 and 24 on pages 139 and 142. The tables should be renumbered 1-7, and the specification amended so that references to these tables are corrected.

Formal Matters

3. The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R."1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 209532 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, page 148).

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 22-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 22-34 are directed to the protein of SEQ ID NO: 50, identified as PRO347. The instant specification discloses that PRO347 is a 455 amino acid protein, and is presumably a membrane-bound protein with a signal sequence from amino acids 1-26, extracellular domain from amino acids 1-109, and transmembrane domain from amino acids 110-124. The specification teaches that PRO347 has significant sequence homology to the cysteine-rich secretory protein-3. However, the protein (or encoding nucleic acids) do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The claims are directed to isolated polypeptides having at least 80% sequence identity to the polypeptide of SEQ ID NO: 50, with or without its signal peptide, or to the extracellular domain of SEQ ID NO: 2 with or without its signal peptide. Dependent claims are directed to chimeric proteins comprising the aforementioned polypeptides. The specification contains numerous asserted utilities for the polypeptide and encoding nucleic acid at pages 69-89, including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight

markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO347 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO347.

The specification teaches that PRO347 has (unspecified) homology to cysteine-rich secretory protein-3. At pages 5, 12, 57 and 80, the specification states that PRO347 is a newly identified cysteine-rich secretory protein-3 homolog, and possesses activity typical of that protein, however no activity is known or disclosed for cysteine-rich secretory protein-3. The amino acid domains of the putative PRO347 peptide is shown in Figure 20 of the specification, in which signal sequence, extracellular and transmembrane domains are identified, however there is no disclosure that the protein is expected to be a transmembrane protein other than identification of a transmembrane domain in Figure 20. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO347. Without any information as to the specific properties of PRO347, the mere identification of such as having significant sequence homology to cysteine-rich secretory protein-3 is not sufficient to impart any particular utility to the claimed polypeptides or encoding nucleic acids.

The specification at pages 119-137 describes experiments in which PRO347 encoding genes (as well as PRO327, PRO344, PRO357 and PRO715) are asserted to be amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. At pages 119-137 it

is disclosed that nucleic acids encoding PRO347 had a ΔCt value of at least 1.0 for a number of primary lung and colon tumors and/or cell lines. At page 120, one delta (Δ) Ct unit is defined as corresponding to 1 PCR cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold, 3 units to 8-fold amplification and so on. The specification further indicates that ΔCt is used as a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results. It is not clear how measurements of hundredths of a PCR cycle can be made, nor what the significance of a difference of 1 or 2 PCR cycles would be.

Results from such experiments are presented in Table 10 on page 137. The only samples shown are from tumors (cell lines?) that appear to be established, LT12-LT21, which on page 122, Table 9 are identified as lung tumor cells. Additionally, the table does not identify which columns are associated with which gene, so it is not shown what results correspond to PRO347, and the numbers do not show any type of recognizable pattern, since many go up and many also go down. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO347 shows a positive correlation with lung and colon cancer, much less that the levels of PRO347 would be diagnostic of such. Even *if* the data demonstrated a slight increase in copy number of PRO347 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not

supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that the PRO347 polypeptide can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO347 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5.1 Claims 22-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Even if the specification were enabling of how to use the PRO347 polypeptide, enablement would not be found commensurate in scope with the claims. Even if there were a patentable use for the protein of SEQ ID NO: 50, variants of 80-99% identity would not be enabled because the specification has not taught one of ordinary skill in the art how to use them or fragments thereof.

5.2 Claims 22-26, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method

of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 50, with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Priority Determination

6. As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. 101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 8/30/01.

Rejections over Prior Art

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 22-26 are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity, respectively, with the extracellular domain (with or without the signal sequence) or full-length protein of SEQ ID NO: 50. Claims 27-32 are drawn to the extracellular domain (with or without the signal sequence) or full-length protein of SEQ ID NO: 50. Claims 33 and 34 encompass chimeric protein comprising the polypeptide of claim 22 fused to a heterologous polypeptide which may be an epitope tag or an Fc region of an immunoglobulin.

7.1 Claims 22-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Botstein et al., WO 99/35170, July 15, 1999. Botstein et al. disclose a protein (SEQ ID NO: 14) that is 100% identical to the amino acid sequence of SEQ ID NO: 50 of the instant application. Botstein et al. also teaches chimeric protein comprising the polypeptide of claim 22 fused to a heterologous polypeptide which may be an epitope tag (page 11, lines 25-32).

7.2 Claims 22-27, 31, 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Holtzman, WO 99/54343, October 28, 1999. Holtzman discloses a protein (SEQ ID NO: 2) that is 96.8% identical to the amino acid sequence of SEQ ID NO: 50 of the instant application, 99% identical to the extracellular domain of SEQ ID NO: 50 and 100% identical to the extracellular domain minus the signal peptide of SEQ ID NO: 50. Holtzman also teaches chimeric protein comprising the polypeptide of claim 22 fused to a heterologous polypeptide which may be a region of an immunoglobulin (page 31).

7.3 Claims 22-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Suzuki et al., Database SPTREMBL_21, Accession No. Q9BE36, June 1, 2001. Claims 22-24 are drawn to polypeptides having at least 80%, 85%, 90%, sequence identity, respectively, with the extracellular domain (with or without the signal sequence) of SEQ ID NO: 50. Suzuki et al. disclose a polypeptide comprising an amino acid sequence that is 92.7% identical to the extracellular domain (amino acids 1-109) of SEQ ID NO: 50.

7.4 Claims 22-27 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Kato et al., WO 01/49728, July 12, 2001. Kato et al. disclose a polypeptide (SEQ ID NO: 5) that is 96.8% identical to the polypeptide of SEQ ID NO: 50 of the instant application, 99% identical to the extracellular domain of SEQ ID NO: 50 and 100% identical to the extracellular domain minus the signal peptide of SEQ ID NO: 50.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Suzuki et al., Database SPTREMBL_21, Accession No. Q9BE36, June 1, 2001, or Kato et al., WO 01/49728, July 12, 2001, either one in view of Hopp et al., U.S. Patent Number 5,011,912.

The teachings of the two primary references are cited above. All of the protein sequences are clearly identified as being from nucleic acid sequence, indicating that the nucleic acids encoding the proteins had been cloned. Neither of the primary references teaches expression of the protein as a fusion protein comprising an epitope tag or Fc region.

Hopp et al. teach the use of an amino acid sequence, "ADYKDDDDK", which is disclosed as being immunogenic, for use in producing fusion protiens which can then be easily

purified. See, for example, column 2, lines 45-57. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the protein of any one of the primary references by producing such as a fusion protein comprising the flag amino acid sequence of Hopp et al., for the purpose of being able to easily purify the proteins of the primary references. The motivation and expectation of success are both taught by Hopp et al. who teach the flag peptide/monoclonal antibody purification system as being generally useful for such.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

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